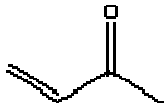
ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
METHYL VINYL KETONE
(CAS Reg. No. 78-94-4)



INTERIM

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PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicology and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described on methyl vinyl ketone at concentrations below the corresponding AEGL.

TABLE OF CONTENTS

LIST OF TABLES

EXECUTIVE SUMMARY

Methyl vinyl ketone (MVK) is a colorless to light yellow liquid at ambient temperature and pressure. It is used in the production of polymer systems to produce plastics and resins and as an intermediate in the production of vitamin A and steroids (HSDB 2003). Domestic production was between 10,000 and 100,000 pounds in 1991. It degrades readily in the atmosphere with a half-life estimated at 21 hours. It is highly irritating to mucous membranes, especially the upper respiratory tract and eyes. Acute lethality data for animal species were sparse. Nonlethal inhalation animal studies indicate that MVK is an irritant and that the upper respiratory tract is the target for toxicity. Irritant effects were seen in studies ranging from a single 6-hour exposure to exposures for 2 to 13 weeks. No one-time exposure studies showing ocular irritation or nasal irritation are available, but eye squinting or closing was observed during repeated inhalation exposure studies in rodents.

The AEGL-1 values are based on the study by Morgan et al. (2000). Five male and five female Fischer-344 rats or $B_6C_3F_1$ mice were exposed to 0, 0.25, 0.5, 1, 2, 4, or 8 ppm MVK 6 hours/day, 5 days/week for a total of 12 exposures. 100% of the rats were found dead or euthanized in moribund condition after a single 6-hour exposure to 8 ppm, and 2/5 male mice died after ten exposures to the same concentration. Exposure related findings in mice were less severe and less widespread than observed in rats. Histological examination of the respiratory tract showed nasal cavity toxicity and lung necrosis in rats, but only nasal cavity lesions in mice, that occurred following exposure to ≥4 ppm in both sexes. Nasal cavity lesions were observed at 1 ppm in rats and mice. A NOAEL of 0.5 ppm was demonstrated for the nasal lesions in both species. These nasal lesions indicate substantial irritant properties with MVK exposure. Indeed, Eastman Kodak (1992, study conducted in 1973) reported immediate clinical signs of irritation in several rodent species exposed to 3.9 and 7.8 ppm (nominal) MVK. Therefore, the point of departure for deriving the AEGL-1 values is irritation with a NOAEL of 0.5 ppm based on slight nasal lesions observed after multiple exposures to 1 ppm in Morgan et al. (2000). No interspecies uncertainty factor was considered necessary since similar NOAELs were obtained in multiple species (rat, mouse, guinea pig, rabbit) in two separate studies. An uncertainty factor of 3 was used for sensitive populations (intraspecies). A factor of 10 was considered unnecessary since the toxic effects of MVK are related to contact irritation and responses are not expected to vary substantially among individuals, or to vary with duration of exposure (NRC, 2001). Therefore, AEGL-1 values were held constant across all time periods.

The AEGL-2 values are also based on the study by Morgan et al. (2000). As discussed above five male and five female Fischer-344 rats or $B_6C_3F_1$ mice were exposed at each of five exposure concentrations. The lowest concentration causing nasal cavity necrosis was 2 ppm in rats and mice, and this exposure concentration was a NOAEL for lung lesions in rats. The toxic effects of MVK are related to contact irritation of the respiratory tract. Nasal necrosis was not regarded in determining the point of departure due to the repeated exposure regimen in this study, but irritation during the first exposure was assumed to precede this tissue damage. Therefore, the AEGL-2 values are based on respiratory tract irritation at 2 ppm that could impair escape for some individuals. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain health protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was

performed using n = 3 when extrapolating to time points ≤6 hours, and n = 1 when extrapolating to longer time points (NRC 2001). In addition, an uncertainty factor of 3 was used for intraspecies extrapolation using the same rationale as for the AEGL-1 values. The 10-minute AEGL-2 value was set equivalent to the 30-minute value due to uncertainties in extrapolating from the experimental exposure durations of ≥4 hours to 10 minutes.

The AEGL-3 values are based on 4 ppm as a point of departure for the lethal effects of MVK (Eastman Kodak 1992; Morgan et al. 2000). 100% of the rats were found dead or euthanized in moribund condition after a single 6-hour exposure to 8 ppm, and 2/5 male mice died after ten exposures to the same concentration. There were no deaths in rats or mice exposed to 4 ppm for 12 days. The study reported by Eastman Kodak (1992, study conducted in 1973) showed 20% mortality in rats after 8 days of exposure to 3.9 ppm (all concentrations nominal), 90% mortality after nine days exposure to 7.8 ppm, but no mortality after 10 days exposure to 2.1 ppm. In this same study there were no deaths in guinea pigs after nine days exposure at either 3.9 or 7.8 ppm, no deaths in rabbits at 7.8 ppm, though 1/3 rabbits died after 9 days exposure to 3.9 ppm. These data on repeated exposure suggest that the lethal effects of MVK do not vary substantially among species and that 4 ppm is a reliable point of departure for deriving AEGL-3 values. As with the AEGL-2 values, the time scaling approach of ten Berge et al. (1986) was used as described above. In addition, an uncertainty factor of 3 was used for intraspecies extrapolation using the same rationale as for the AEGL-1 values. Responses will not vary substantially among individuals, and do not appear to vary substantially among species since the dose-response relationship was similar in rats, rabbits, guinea pigs, and mice. The 10-minute AEGL-2 value was set equivalent to the 30-minute value due to uncertainties in extrapolating from the experimental exposure durations of 6 hours to 10 minutes.

The calculated AEGL values are listed in Table 1.

TABLE 1. Summary of AEGL Values for Methyl vinyl ketone

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	NOAEL for respiratory tract irritation (Morgan et al. 2000)
AEGL–2 (Disabling)	1.5 ppm (4.4 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.2 ppm (3.5 mg/m^3)	0.76 ppm (2.2 mg/m^3)	0.50 ppm (1.5 mg/m^3)	LOAEL for respiratory tract irritation (Morgan et al. 2000)
AEGL–3 (Lethal)	3.1 ppm (9.0 mg/m^3)	3.1 ppm (9.0 mg/m^3)	2.4 ppm (7.0 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.0 ppm (2.9 mg/m^3)	Lethality at 4 ppm (Eastman Kodak 1992; Morgan et al. 2000)

References

Eastman Kodak. 1992. Initial submission: Letter from Eastman Kodak to USEPA regarding toxicity studies of 3-buten-2-one conducted in 1973 with attachments and cover letter dated 9/02/92. Doc #88-920008988.

Morgan, D.L., H.C. Price, R.W. O'Conner et al. 2000. Upper respiratory tract toxicity of inhaled methylvinyl ketone in F-344 rats and B6C3F1 mice. Toxicol. Sci 58:182-194.

NRC (National Research Council). 2001. Standing Operating Procedures for Developing Acute Exposure Guideline Levels for Hazardous Chemicals. National Academy Press, Washington, DC.

ten Berge, W.F., Zwart, A. and Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. *Journal of Hazardous Materials*. 13:301-309.

1. INTRODUCTION

MVK is a colorless to light yellow liquid at ambient temperature and pressure. It is highly irritating to mucous membranes, especially the upper respiratory tract and eyes (HSDB 2003). Domestic production was between 10,000 and 100,000 pounds in 1991 and it is used in the production of polymer systems to produce plastics and resins. It is an intermediate in the production of vitamin A and steroids. It degrades readily in the atmosphere with a half-life estimated at 21 hours. The chemical structure is given below and a summary of the chemical and physical properties are given in Table 2.

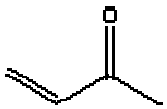

TABLE 2. Chemical and Physical Properties of MVK

Parameter	Value	References
Synonyms	Butanone, methylvinylketon, methylene acetone, acetyl ethylene	HSDB 2003
Chemical formula	C_4H_6O	O'Neil et al. 2001
Molecular weight	70.09	O'Neil et al. 2001
CAS Reg. No.	78-94-4	HSDB 2003
Physical state	liquid	O'Neil et al. 2001
Solubility in water	>10%	HSDB 2003
Vapor pressure	83.9 mm Hg at 25 ^oC	HSDB 2003
Vapor density (air =1)	2.41	HSDB 2003
Liquid density (water =1)	0.8636 at 20 ^oC	HSDB 2003
Melting point	-7 ^oC	HSDB 2003
Boiling point	81.4 ^oC	HSDB 2003
Explosive limits	2.1 – 15.6 vol. %	IPCS 2003
Conversion factors	1 ppm = 2.91 mg/m^3 1 mg/m^3 = 0.34 ppm	HSDB 2003

2. HUMAN TOXICITY DATA

2.1. Acute Lethality

No studies are reported in the literature.

2.2. Nonlethal Toxicity

No case studies are reported in the literature. MVK is suspected of causing conjunctivitis and injury to the corneal epithelium of synthetic rubber workers in Czechoslovakia (Grant 1986). Its odor is pungent with a reported threshold of 0.2 ppm (HSDB 2003).

2.3. Neurotoxicity

No studies are reported in the literature.

2.4. Developmental/Reproductive Toxicity

No studies are reported in the literature.

2.5. Genotoxicity

No studies are reported in the literature.

2.6. Carcinogenicity

No studies are reported in the literature.

2.7. Summary

No studies are reported in the literature.

3. ANIMAL TOXICITY DATA

The animal toxicity data are summarized in Table 3.

TABLE 3. MVK Toxicity : Inhalation Exposure in Animals				
Species	**Exposure time**	**Concentration (ppm)**	**Endpoint**	**Reference**
Rat	6 hr/day, 9 days	2.1, 3.9, 7.8 nominal	2.1 ppm = NOAEL 3.9 ppm = 20% mortality (2/10) after 8 days, eye irritation 7.8 ppm = 90% mortality within 9 days, eye irritation	Eastman Kodak 1992
Guinea pig	6 hr/day, 9 days	2.1, 3.9, 7.8 nominal	2.1 ppm = NOAEL 3.9 ppm = airway lesions (6/6) , eye irritation 7.8 ppm = airway lesions (6/6); 5/6 acute pneumonitis, eye irritation	Eastman Kodak 1992
Rabbit	6 hr/day, 9 days	2.1, 3.9, 7.8 nominal	2.1 ppm = NOAEL 3.9 ppm = 1/3 mortality within 9 days, eye irritation 7.8 ppm = 3/3 acute pneumonitis, no mortality, eye irritation	Eastman Kodak 1992
Rat	6 hr/day, 5days/wk for 12 days	0.25, 0.5, 1, 2, 4, 8	0.5 ppm = NOAEL 1 ppm = LOAEL for slight nasal lesions 2 ppm = nasal cavity necrosis; no lung lesions 4 ppm = nasal cavity and lung necrosis 8 ppm = 100% mortality (10/10) after 1 day exposure	Morgan et al. 2000
Mouse	6 hr/day, 5days/wk for 12 days	0.25, 0.5, 1, 2, 4, 8	0.5 ppm = NOAEL 1 ppm = LOAEL for slight nasal lesions 2 ppm = nasal cavity necrosis 4 ppm = nasal cavity necrosis 8 ppm = 20% mortality (2/10) after 10 days exposure, nasal cavity and lung necrosis.	Morgan et al. 2000
Rat	6 hr/day, 5days/wk for 13 wk	0.5, 1, 2	0.5 ppm = LOAEL for nasal lesions	Morgan et al. 2000
Mouse	6 hr/day, 5days/wk for 13 wk	0.5, 1, 2	0.5 ppm = NOAEL 1 ppm = LOAEL for nasal lesions Decreased leukocytes in males at all dose levels	Morgan et al. 2000
Mouse	Not specified	Not specified	5.2 ppm = RD_{50} for sensory irritation capacity	Muller and Gref 1984

3.1. Acute Lethality

3.1.1. Rodents

Morgan et al. (2000) conducted whole-body inhalation exposures of rats and mice. Five male and five female Fischer-344 rats or $B_6C_3F_1$ mice were exposed to 0, 0.25, 0.5, 1, 2, 4, or 8 ppm MVK 6 hours/day, 5 days/week for a total of 12 exposures (purity 99%). Exposure levels were monitored at 2.5 minute intervals by gas chromatography and were within $\pm$ 10% of the target concentration. The authors reported a 100% incidence of rats found dead or euthanized in moribund condition after a single exposure to 8 ppm MVK, and 2/5 male mice died after ten exposures to this concentration. Death was attributed to airway necrosis. There were no deaths in rats or mice exposed to 4 ppm for 12 days.

The whole-body inhalation study reported by Eastman Kodak (1992 , study conducted in 1973) showed 20% mortality in rats after 8 days of exposure to 3.9 ppm (nominal), 90%

mortality after nine days exposure to 7.8 ppm, but no mortality on the day following 9 days exposure to 2.1 ppm. In this same study there were no deaths in guinea pigs after nine days exposure at either 3.9 or 7.8 ppm, no deaths in rabbits at 7.8 ppm, though 1/3 rabbits died after 9 days exposure to 3.9 ppm. Severe airway necrosis was found in all animals exposed to 7.8 ppm and a less severe inflammation was observed at the intermediate exposure concentration. A high percentage of control animals exhibited mild chronic bronchitis or pneumonitis which was also observed in the low dose group of animals. Chamber concentrations were measured in separate experiments with animals using gas chromatography after collecting chamber atmosphere samples in cyclohexanone. The mean of four measured concentrations for the high concentration chamber (7.8 ppm nominal) was 5.15 ppm, and 1.74 ppm for the low concentration (2.1 ppm nominal). No separate study to estimate actual exposure concentrations was conducted for the 3.9 ppm (nominal) exposure.

Results of the Morgan et al. (2000) and Eastman Kodak (1992) studies suggest that the lethal effects of MVK do not vary among species. From a risk assessment standpoint, humans are often less susceptible to chemicals that cause site-specific nasal effects in rodents due largely to anatomical differences. The nasal surface area in rodents relative to body weight is much higher, and other physiologic and toxicodynamic differences influence their response to inhaled materials as compared to people (Miller 1995).

RTECS (2006) reports an LC_{50} in rats of 2.4 ppm after a 4-hour exposure and an LC_{50} in mice of 2.8 ppm after a 2-hour exposure, but these data reported in 1982 could not be obtained and evaluated.

3.2. Nonlethal Toxicity

3.2.1. Rats

In a 2-week inhalation exposure study in Fischer-344 rats, animals exposed to 0.5 ppm or less showed no adverse effects (Morgan et al. 2000). Animals were exposed to 0, 0.25, 0.5, 1, 2, 4, or 8 ppm MVK 6 hours/day, 5 days/week for a total of 12 exposures. Exposure levels were monitored at 2.5 minute intervals by gas chromatography. Clinical signs of toxicity were not reported. Two ppm caused lesions of the respiratory tract that included necrosis and squamous metaplasia of olfactory and respiratory epithelium in the nasal cavity but no lung lesions. Exposure to 4 ppm MVK caused epithelial necrosis and metaplasia in the lower airways of the lung in addition to lesions of the nasal cavity. At 1 ppm, exposure-related lesions were limited to the anterior nasal cavity and consisted of mild squamous metaplasia of the respiratory/transitional epithelium. Body weights of males and females at the 2 ppm exposure concentration and above were significantly less than those of controls by 4 days of exposure, and the differences continued throughout the remainder of the 2-week study. The NOAEL was 0.5 ppm.

Morgan et al. (2000) exposed Fischer-344 rats (10/group/sex) to MVK, 6 hr/day, 5 days/week for 13 weeks by inhalation at 0.5, 1, and 2 ppm. Clinical signs of toxicity were not reported. Body weights of both males and females at 2 ppm were significantly less than controls after one week of exposure and the difference continued throughout the remainder of the 13-week study. Leukocyte counts were significantly decreased in male rats exposed to 2 ppm. Treatment-related lesions were evident in the nose in males and females by day 21 at the 1 and 2

ppm exposure concentrations. The lesions were characterized by patchy areas of respiratory epithelial degeneration and necrosis of the nasal cavity. After 13 weeks of treatment the distribution of lesions was similar to that of day 21, but they were less severe. Examination of sperm motility and vaginal smears revealed no difference between treated and control rats. The NOAEL was 0.5 ppm.

3.2.2. Mice

In a 2-week inhalation exposure study, $B_6C_3F_1$ mice exposed to 0.5 ppm or less showed no adverse effects (Morgan et al. 2000). Animals were exposed to 0, 0.25, 0.5, 1, 2, 4, or 8 ppm MVK 6 hours/day, 5 days/week for a total of 12 exposures. Exposure levels were monitored at 2.5 minute intervals by gas chromatography. Clinical signs of toxicity were not reported. Two ppm caused lesions of the respiratory tract that included necrosis of respiratory epithelium in the nasal cavity. At 1 ppm exposure-related histopathology was less severe and less widespread than that observed in rats. Body weight of both male and female mice at the 2 ppm exposure concentration and above were significantly less than controls by 4 days of exposure. This difference continued throughout the remainder of the 2-week study. The NOAEL was 0.5 ppm.

Morgan et al. (2000) exposed $B_6C_3F_1$ mice (10/group/sex) to MVK, 6 hr/day, 5 days/week for 13 weeks by inhalation at 0.5, 1, and 2 ppm. Clinical signs of toxicity were not reported. Body weight of neither males nor females was different from controls throughout the 13-week study. Leukocyte counts were significantly decreased in male mice at all exposure concentrations. This effect was attributed to significant decreases in lymphocytes and neutrophil counts. There was no correlating histopathology in the hemopoietic tissues. Treatment-related lesions were evident in the nose in males and females at 2 ppm. The lesions were characterized by squamous metaplasia of the transitional and respiratory epithelium on the tips of the naso- and maxilloturbinates. These lesions were minimal in severity, and no treatment related lesions were identified in the larynx or lung. Examination of sperm motility and vaginal smears revealed no difference between treated and control mice. The NOAEL was 0.5 ppm.

Muller and Gref (1984) reported RD_{50} data for sensory irritation capacity in mice on ketones, alcohols, acetates, and benzene derivatives. The RD_{50} of 5.2 ppm for MVK was based on unpublished data and only sparse methodology was provided, which limits its usefulness in the AEGL determination process.

3.2.3. Other Rodent Studies

Eastman Kodak (1992, study conducted in 1973) reported whole-body inhalation exposures of male rats (10), male guinea pigs (6), and male rabbits (3) to nominal concentrations of 2.1, 3.9, and 7.8 ppm MVK, 6 hours/day for 9 days (interrupted or consecutive days was not specified). Chamber concentrations were measured in separate experiments with animals using gas chromatography after collecting chamber atmosphere samples in cyclohexanone. The mean of four measured concentrations for the high concentration chamber (7.8 ppm nominal) was 5.15 ppm, and 1.74 ppm for the low concentration (2.1 ppm nominal). No separate study to estimate actual exposure concentrations was conducted for the 3.9 ppm (nominal) exposure. The high exposure level of MVK produced immediate nose rubbing and eye irritation within five minutes (blinking and lacrimation), dyspnea in 4 hours, and slight to moderate weakness and wheezing

post exposure in all animals. MVK at 3.9 ppm (nominal) produced nose rubbing and eye irritation (blinking and lacrimation) within five minutes in all animals. MVK at 2.1 ppm produced no clinical signs of toxicity. Mortality during the animal study was discussed above (Acute Studies, Section 3.1). Terminal body weight was significantly affected in rats at 3.9 ppm (high mortality at 7.8 ppm precluded comparison with controls). Severe airway necrosis was found in all animals exposed to 7.8 ppm and a less severe inflammation was observed at the intermediate concentration. All rats at 3.9 ppm exhibited acute pneumonitis, eight had acute tracheitis, and two had testicular atrophy. Acute tracheitis was observed in one rat at 2.1 ppm, but this was also seen in 1/15 control rats. Histopathology in guinea pigs and rabbits had a pattern similar to that seen in rats.

3.3. Developmental/Reproductive Toxicity

No studies are reported in the literature.

3.4. Genotoxicity

Only *in vitro* mutagenicity data are available on methyl vinyl ketone and the results are mixed. It was positive in *Salmonella typhimurium* strain TA100 (Eder et al. 1990, 1993, 1994) without S-9 activation, but negative in TA98 (Zeiger et al. 1992) and TA102 (Jung et al. 1992), and negative with activation in TA2638 (Watanabe et al. 1998). However, Zeiger et al. 1992 showed that it was negative in TA100 without activation and positive with activation. Neudecker et al. (1989) showed that the addition of S-9 activation reduced methyl vinyl ketone mutagenicity, but increased mutagenic activity when epoxide hydrolase activity was inhibited. Several studies have shown methyl vinyl ketone to be weakly active in the SOS chromotest (Eder et al. 1990, 1993, 1994). Weak genotoxic activity was indicated in the Drosophilia eye mosaic assay (Vogel and Nivard 1993).

3.5. Chronic Toxicity/Carcinogenicity

No studies are reported in the literature.

3.6. Summary

Acute lethality data for animal species were sparse. Nonlethal inhalation animal studies indicate that MVK is a contact irritant at the point of entry and the upper respiratory tract is the target for toxicity. Irritant effects were evident from study durations of a single 6-hour exposure to exposure times of 2 to 13 weeks. At higher concentrations lesions of the upper airways were evident. Genotoxicity data are equivocal. There are no data on reproductive/developmental toxicity or carcinogenicity.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

No studies on the metabolism and disposition of MVK were available in the literature. Ketones are known to undergo metabolic transformation to the corresponding alcohols, diols,

epoxides and various other metabolites (NTP 2005). Ketones are known to react reversibly with glutathione.

4.2. Mechanism of Toxicity

MVK is a direct acting irritant on mucous membranes and is noted as a severe irritant to skin, eyes, and the respiratory system (HSDB 2003).

4.3. Structure Activity Relationships

MVK is part of a group of unsaturated compounds structurally related to acrolein, a known mutagen (NTP 2005).

4.4. Other Relevant Information

4.4.1. Species Variability

Studies in rats, mice, Guinea pigs, and rabbits (Table 3) do not indicate much variability among species to the sublethal effects of MVK. This is likely due to the direct irritating effect of the chemical on airways. The rat appeared somewhat more sensitive than the mouse, possibly due to differences in breathing patterns, as well as anatomical differences and airflow patterns (Morgan 2000).

4.4.2. Concentration-Exposure Duration Relationship

The toxic effects of MVK are related to contact irritation to the upper respiratory tract. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain health-protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling may be performed using n=3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC, 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No appropriate human data are available for deriving AEGL-1 values.

5.2. Summary of Animal Data Relevant to AEGL-1

Inhaled MVK is a contact irritant with 0.5 ppm as a NOAEL and 1 ppm as a LOAEL for nasal cavity lesions in rats and mice following about 2 weeks of exposure (6 hr/day, 5days/wk for 12 days; Morgan et al. 2000). These nasal lesions indicate substantial irritant properties with MVK exposure. The data reported in Eastman Kodak (1992) on rat, mouse, guinea pig, and rabbit corroborate these findings.

5.3. Derivation of AEGL-1 Values

The AEGL-1 values (Table 4) are based on the study by Morgan et al. (2000). Five male and five female Fischer-344 rats or $B_6C_3F_1$ mice were exposed to 0, 0.25, 0.5, 1, 2, 4, or 8 ppm methyl vinyl ketone (MVK) 6 hours/day, 5 days/week for a total of 12 exposures. A 100% incidence of mortality was observed in rats after a single exposure to 8 ppm and in 2/5 male mice after ten exposures to the same concentration. Exposure related findings in mice were less severe and less widespread than observed in rats. Histological examination of the respiratory tract showed nasal cavity toxicity and lung necrosis in rats, but only nasal cavity lesions in mice, that occurred following exposure to ≥4 ppm in both sexes. Nasal cavity lesions were observed at 1 ppm in rats and mice. A NOAEL of 0.5 ppm was demonstrated for the nasal lesions in both species. These nasal lesions indicate substantial irritant properties with MVK exposure. Indeed, Eastman Kodak (1992, study conducted in 1973) reported immediate clinical signs of irritation in several rodent species (rat, mouse, guinea pig, rabbit) exposed to 3.9 and 7.8 ppm (nominal) MVK. Therefore, the point of departure for deriving the AEGL-1 values is irritation with a NOAEL of 0.5 ppm based on slight nasal lesions observed after multiple exposures to 1 ppm (Morgan et al. (2000). No interspecies uncertainty factor was considered necessary since similar NOAELs were obtained in multiple species in two separate studies. An uncertainty factor of 3 was used for sensitive populations (intraspecies). A factor of 10 was considered unnecessary since the toxic effects of MVK are related to contact irritation and responses are not expected to vary substantially among individuals, or to vary with duration of exposure (NRC, 2001). Therefore, AEGL-1 values were held constant across all time periods.

TABLE 4. AEGL-1 Values for MVK

10-min	30-min	1-h	4-h	8-h
0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No appropriate human data are available for deriving AEGL-2 values.

6.2. Summary of Animal Data Relevant to AEGL-2

Data on rats show that the lowest concentration of inhaled MVK causing nasal cavity necrosis was 2 ppm in rats and mice following about 2 weeks of exposure (6 hr/day, 5days/wk for 12 days; Morgan et al. 2000). Irritation to the respiratory tract presumably occurred prior to this tissue damage. The data in Eastman Kodak (1992) reporting clinical signs of irritation during inhalation exposures of rats, mice, guinea pigs, and rabbits support this approach.

6.3. Derivation of AEGL-2 Values

The AEGL-2 values (Table 5) are based on the study by Morgan et al. (2000). As discussed in Section 5.3 five male and five female Fischer-344 rats or $B_6C_3F_1$ mice were exposed at each of five exposure concentrations for 6 hr/day, 5 days/week for 12 days. The lowest concentration causing nasal cavity necrosis was 2 ppm in rats and mice, and this exposure concentration was a NOAEL for lung lesions in rats. The toxic effects of MVK are related to

contact irritation of the respiratory tract. Nasal necrosis was not regarded in determining the point of departure for the AEGL-2 values due to the repeated exposure regimen in this study, but irritation during the first exposure was assumed to precede the tissue damage. Therefore, the AEGL-2 values are based on respiratory tract irritation at 2 ppm that could impair escape for some individuals. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain health protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to time points ≤6 hours, and n = 1 when extrapolating to longer time points (NRC 2001). An uncertainty factor of 3 was used for intraspecies extrapolation using the same rationale as for the AEGL-1 values. The 10-minute AEGL-2 value was set equivalent to the 30-minute values due to uncertainties in extrapolating from the experimental exposure durations of 4 hours and greater.

TABLE 5. AEGL-2 Values for MVK

10-min	30-min	1-h	4-h	8-h
1.5 ppm (4.4 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.2 ppm (3.5 mg/m^3)	0.76 ppm (2.2 mg/m^3)	0.50 ppm (1.5 mg/m^3)

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No appropriate human data are available for deriving AEGL-3 values.

7.2. Summary of Animal Data Relevant to AEGL-3

RTECS (2006) reports an LC_{50} in rats of 2.4 ppm after a 4-hour exposure and an LC_{50} in mice of 2.8 ppm after a 2-hour exposure, but these data reported in 1982 could not be obtained and evaluated. Morgan et al. (2000) observed 100% mortality in rats (found dead or euthanized in moribund condition) after a single 6-hour exposure to 8 ppm, and 2/5 male mice died after ten exposures to the same concentration. There were no deaths in rats or mice exposed to 4 ppm for 12 days. The study reported by Eastman Kodak (1992, study conducted in 1973) showed 20% mortality in rats after 8 days of exposure to 3.9 ppm (nominal), 90% mortality after nine days exposure to 7.8 ppm (nominal), but no mortality after 10 days exposure to 2.1 ppm (nominal). In this same study there were no deaths in guinea pigs after nine days exposure at either 3.9 or 7.8 ppm, no deaths in rabbits at 7.8 ppm, though 1/3 rabbits died after 9 days exposure to 3.9 ppm.

7.3. Derivation of AEGL-3 Values

The AEGL-3 values (Table 6) are based on 4 ppm as a point of departure for the lethal effects of MVK (Eastman Kodak 1992; Morgan et al. 2000). 100% of the rats were found dead or euthanized in moribund condition after a single 6-hour exposure to 8 ppm, and 2/5 male mice died after ten exposures to the same concentration (Morgan et al. 2000). There were no deaths in rats or mice exposed to 4 ppm for 12 days. The study reported by Eastman Kodak (1992, study conducted in 1973) showed 20% mortality in rats after 8 days of exposure to 3.9 ppm (all concentrations nominal), 90% mortality after nine days exposure to 7.8 ppm, but no mortality

after 10 days exposure to 2.1 ppm. In this same study there were no deaths in guinea pigs after nine days exposure at either 3.9 or 7.8 ppm, no deaths in rabbits at 7.8 ppm, though 1/3 rabbits died after 9 days exposure to 3.9 ppm. These data on repeated exposure suggest that the lethal effects of MVK do not vary substantially among species and that 4 ppm is a reliable point of departure for deriving AEGL-3 values. The concentration-exposure time relationship for many irritant and systemically-acting vapors and gases may be described by $C^n \times t = k$, where the exponent, n, ranges from 0.8 to 3.5 (ten Berge et al., 1986). To obtain health protective AEGL values in the absence of an empirically derived chemical-specific scaling exponent, temporal scaling was performed using n = 3 when extrapolating to time points ≤6 hours, and n = 1 when extrapolating to longer time points (NRC 2001). An uncertainty factor of 3 was used for intraspecies extrapolation using the same rationale as for the AEGL-1 values. Responses will not vary substantially among individuals, and do not appear to vary substantially among species since the dose-response relationship was similar in rats, rabbits, guinea pigs, and mice (all four species demonstrated escalating respiratory tract lesions after about 2 weeks of exposure to a concentration range of 2 – 8 ppm and mortality was observed in three of the four species at the higher concentrations; Table 3). The 10-minute AEGL-3 value was set equivalent to the 30-minute value due to uncertainties in extrapolating from the experimental exposure durations of 6 hours to 10 minutes.

TABLE 6. AEGL-3 Values for MVK

10-min	30-min	1-h	4-h	8-h
3.1 ppm (9.0 mg/m^3)	3.1 ppm (9.0 mg/m^3)	2.4 ppm (7.0 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.0 ppm (2.9 mg/m^3)

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

The AEGL-1 values are based on the study by Morgan et al. (2000) in which respiratory tract irritation is strongly implied by nasal cavity and lung lesions in both rats and mice.

The AEGL-2 values are based on the study by Morgan et al. (2000) in which respiratory tract irritation of an escape-impairing nature is strongly implied by nasal cavity and lung lesions in both rats and mice.

The AEGL-3 values are based on the lethal effects of MVK (Eastman Kodak 1992; Morgan et al. 2000) in rats, mice, and rabbits.

TABLE 7. Summary of AEGL Values for MVK

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL–1 (Nondisabling)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)
AEGL–2 (Disabling)	1.5 ppm (4.4 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.2 ppm (3.5 mg/m^3)	0.76 ppm (2.2 mg/m^3)	0.50 ppm (1.5 mg/m^3)

AEGL–3 (Lethal)	3.1 ppm (9.0 mg/m^3)	3.1 ppm (9.0 mg/m^3)	2.4 ppm (7.0 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.0 ppm (2.9 mg/m^3)

8.2. Comparison with Other Standards and Guidelines

ACGIH (2006) has listed a ceiling value for MVK of 0.2 ppm which appears to be based on potential sensitization in workers after repeated occupational exposures.

TABLE 8. Extant Standards and Guidelines for MVK

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)
AEGL-2	1.5 ppm (4.4 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.2 ppm (3.5 mg/m^3)	0.76 ppm (2.2 mg/m^3)	0.50 ppm (1.5 mg/m^3)
AEGL-3	3.1 ppm (9.0 mg/m^3)	3.1 ppm (9.0 mg/m^3)	2.4 ppm (7.0 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.0 ppm (2.9 mg/m^3)
TLV-C (ACGIH)[a]	0.2 ppm				

[a]ACGIH TLV-C (Threshold Limit Value - Ceiling) (ACGIH 2006); is defined as the concentration that should not be exceeded at any time during the work day

8.3. Data Adequacy and Research

Human data appropriate for derivation of AEGL values were not available. Sparse animal lethality data were available for derivation of AEGL-3 values, although adequate data for deriving AEGL-1 and AEGL-2 values were available. Single exposure data were practically nonexistent.

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APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

Key Study: Morgan et al. (2000)

Toxicity endpoint: Respiratory tract irritation based on nasal cavity lesions from repeated exposure (NOAEL = 0.5 ppm)

Time scaling: None

Uncertainty factors: 3 for intraspecies variability.

Modifying factor: None

Calculations:

10-minute AEGL-1: 0.5 ppm) 3 = 0.17 ppm

30-minute AEGL-1: 0.5 ppm) 3 = 0.17 ppm

1-hour AEGL-1: 0.5 ppm) 3 = 0.17 ppm

4-hour AEGL-1: 0.5 ppm) 3 = 0.17 ppm

8-hour AEGL-1: 0.5 ppm) 3 = 0.17 ppm

Derivation of AEGL-2

Key Studies: Morgan et al. (2000)

Toxicity endpoints: Respiratory tract irritation based on lowest concentration (2.0 ppm) causing nasal cavity necrosis from repeated exposure.

Time scaling: $C^n \times t = k$, where n = 3 when extrapolating to time points ≤6 hours, and n = 1 when extrapolating to longer time points

10-min, 30-min, 1-hr, 4hr

$C^3 \times t = k$

$(2 \text{ ppm})^3 \times 6 \text{ hr} = 48 \text{ ppm·hr}$

8-hr

$C^1 \times t = k$

$(2 \text{ ppm})^1 \times 6 \text{ hr} = 12 \text{ ppm·hr}$

Uncertainty factors: 3 for intraspecies variability.

Modifying factor: None

Calculations:

10-minute AEGL-2: 1.5 ppm (same as 30-minute AEGL-2)

30-minute AEGL-2: $C^3 \times 0.5 \text{ hr} = 48 \text{ ppm·hr}$
$C^3 = 96$
$C = 4.6 \text{ ppm}$
AEGL-2 = 4.6 ppm) 3 = 1.5 ppm

1-hour AEGL-2: $C^3 \times 1 \text{ hr} = 48 \text{ ppm·hr}$
$C^3 = 48$
$C = 3.6 \text{ ppm}$
AEGL-2 = 3.6 ppm) 3 = 1.2 ppm

4-hour AEGL-2: $C^3 \times 4 \text{ hr} = 48 \text{ ppm·hr}$
$C^3 = 12$
$C = 2.3 \text{ ppm}$
AEGL-2 = 2.3 ppm) 3 = 0.76 ppm

8-hour AEGL-2: $C^1 \times 8 \text{ hr} = 12 \text{ ppm·hr}$
$C^1 \times 8 \text{ hr} = 12 \text{ ppm·hr}$
$C = 1.5 \text{ ppm}$
AEGL-2 = 1.5 ppm) 3 = 0.50 ppm

Derivation of AEGL-3

Key Studies: Eastman Kodak 1992; Morgan et al. 2000

Toxicity endpoint: Lethality point of departure = 4 ppm. Morgan et al. (2000) observed a 100% incidence of mortality (dead or euthanized in moribund condition) in rats after a single 6-hour exposure to 8 ppm MVK, and 2/5 male mice died at this concentration after 10 days of exposure. Eastman Kodak (1992, study conducted in 1973) showed 20% mortality in rats after 8 days of exposure to 3.9 ppm (nominal), 90% mortality after nine days exposure to 7.8 ppm (nominal), but no mortality after 10 days exposure to 2.1 ppm (nominal).

Time scaling: $C^n \times t = k$, where n = 3 when extrapolating to time points ≤6 hours, and n = 1 when extrapolating to longer time points

<u>10-min, 30-min, 1-hr, 4hr</u>

$C^3 \times t = k$

$(4 \text{ ppm})^3 \times 6 \text{ hr} = 384 \text{ ppm·hr}$

<u>8-hr</u>

$C^1 \times t = k$

$(4 \text{ ppm})^1 \times 6 \text{ hr} = 24 \text{ ppm·hr}$

Uncertainty factors: 3 for intraspecies variability.

Modifying factor: None

<u>10-minute AEGL-3</u>: 3.1 ppm (same as 30-minute AEGL-3)

<u>30-minute AEGL-3</u>: $C^3 \times 0.5 \text{ hr} = 384 \text{ ppm·hr}$

$C^3 = 768$

$C = 9.16 \text{ ppm}$

$\text{AEGL-3} = 9.16 \text{ ppm} \sqrt[3]{} = 3.1 \text{ ppm}$

<u>1-hour AEGL-3</u>: $C^3 \times 1 \text{ hr} = 384 \text{ ppm·hr}$

$C^3 = 384$

$C = 7.26 \text{ ppm}$

$\text{AEGL-3} = 7.26 \text{ ppm} \sqrt[3]{} = 2.4 \text{ ppm}$

<u>4-hour AEGL-3</u>: $C^3 \times 4 \text{ hr} = 384 \text{ ppm·hr}$

$C^3 = 96$

$C = 4.6 \text{ ppm}$

$\text{AEGL-3} = 4.6 \text{ ppm} \sqrt[3]{} = 1.5 \text{ ppm}$

8-hour AEGL-3: $C^1 \times 8 \text{ hr} = 24 \text{ ppm·hr}$
$C^1 \times 8 \text{ hr} = 24 \text{ ppm·hr}$
$C = 3 \text{ ppm}$
AEGL-3 = 3 ppm) 3 = 1.0 ppm

APPENDIX B: Derivation Summary for Methyl Vinyl Ketone AEGLs

ACUTE EXPOSURE GUIDELINE LEVELS FOR
METHYL VINYL KETONE (CAS Reg. No. 78-94-4)
DERIVATION SUMMARY

AEGL-1 VALUES

10-min	30-min	1-h	4-h	8-h
0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)	0.17 ppm (0.49 mg/m^3)
Key Reference: Morgan, D.L., H.C. Price, R.W. O'Conner et al. 2000. Upper respiratory tract toxicity of inhaled methylvinyl ketone in F-344 rats and B6C3F1 mice. Toxicol. Sci 58:182-194.				
Test Species/Strain/Number: 5 male and 5 female Fischer-344 rats and $B_6C_3F_1$ mice				
Exposure Route/Concentrations/Durations: Inhalation; 0, 0.25, 0.5, 1, 2, 4, or 8 ppm methyl vinyl ketone (MVK) 6 hours/day, 5 days/week for a total of 12 exposures				
Effects: Rat 0.5 ppm = NOAEL 1 ppm = LOAEL for slight nasal lesions 2 ppm = nasal cavity necrosis; no lung lesions 4 ppm = nasal cavity and lung necrosis 8 ppm = 100% mortality (10/10 dead or euthanized in moribund condition) after 1 day exposure Effects: Mouse 0.5 ppm = NOAEL 1 ppm = LOAEL for slight nasal lesions 2 ppm = nasal cavity necrosis 4 ppm = nasal cavity necrosis 8 ppm = 20% mortality (2/10) after 10 days exposure, nasal cavity and lung necrosis.				
Endpoint/Concentration/Rationale: Point of departure = 0.5 ppm. Histological examination of the respiratory tract showed nasal cavity toxicity and lung necrosis in rats at 4 ppm, but only nasal cavity lesions in mice. These nasal lesions indicate substantial irritant properties with MVK exposure. A NOAEL of 0.5 ppm was demonstrated for the nasal lesions in both species, and it is also considered the NOAEL for respiratory tract irritation.				
Uncertainty Factors/Rationale: Uncertainty factor of 3 was used for intraspecies variability. A factor of 10 was considered unnecessary since the toxic effects of MVK are related to contact irritation. Responses will not vary substantially among individuals, and do not appear to vary substantially between species since the dose-response relationship was similar in both rats and mice. This is typical for agents that cause irritant effects. Total uncertainty factor: 3 Interspecies: 1 Intraspecies: 3				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: None				
Time Scaling: None				
Data Adequacy: The same value was applied to all time points from 10 minutes to 8 hours because mild irritation is not expected to vary over time.				

AEGL-2 VALUES

10-min	30-min	1-h	4-h	8-h
1.5 ppm (4.4 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.2 ppm (3.5 mg/m^3)	0.76 ppm (2.2 mg/m^3)	0.50 ppm (1.5 mg/m^3)
Key Reference: Morgan, D.L., H.C. Price, R.W. O'Conner et al. 2000. Upper respiratory tract toxicity of inhaled methylvinyl ketone in F-344 rats and B6C3F1 mice. Toxicol. Sci 58:182-194.				
Test Species/Strain/Number: 5 male and 5 female Fischer-344 rats and $B_6C_3F_1$ mice				
Exposure Route/Concentrations/Durations: Inhalation; 0, 0.25, 0.5, 1, 2, 4, or 8 ppm methyl vinyl ketone (MVK) 6 hours/day, 5 days/week for a total of 12 exposures				
Effects: Rat 0.5 ppm = NOAEL 1 ppm = LOAEL for slight nasal lesions 2 ppm = nasal cavity necrosis; no lung lesions 4 ppm = nasal cavity and lung necrosis 8 ppm = 100% mortality (10/10 dead or euthanized in moribund condition) after 1 day exposure Effects: Mouse 0.5 ppm = NOAEL 1 ppm = LOAEL for slight nasal lesions 2 ppm = nasal cavity necrosis 4 ppm = nasal cavity necrosis 8 ppm = 20% mortality (2/10) after 10 days exposure, nasal cavity and lung necrosis.				
Endpoint/Concentration/Rationale: Point of departure = 2 ppm. Toxic effects of MVK are related to contact irritation of the respiratory tract. Nasal necrosis was not regarded in determining the point of departure due to the repeated exposure regimen in the key study, but irritation during the first exposure was assumed to precede this tissue damage. Therefore, the point of departure is based on the LOAEL for respiratory tract irritation at 2 ppm that may impair escape.				
Uncertainty Factors/Rationale: Uncertainty factor of 3 was used for intraspecies variability. A factor of 10 was considered unnecessary since the toxic effects of MVK are related to contact irritation. Responses will not vary substantially among individuals, and do not appear to vary substantially between species since the dose-response relationship was similar in both rats and mice. This is typical for agents that cause irritant effects. Total uncertainty factor: 3 Interspecies: 1 Intraspecies: 3				
Modifying Factor: None				
Animal to Human Dosimetric Adjustment: None				
Time Scaling: Temporal scaling was performed using n = 3 when extrapolating to time points ≤6 hours, and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).				
Data Adequacy: Well conducted animal study				

AEGL-3 VALUES

10-min	30-min	1-h	4-h	8-h
3.1 ppm (9.0 mg/m^3)	3.1 ppm (9.0 mg/m^3)	2.4 ppm (7.0 mg/m^3)	1.5 ppm (4.4 mg/m^3)	1.0 ppm (2.9 mg/m^3)

Key References: Morgan, D.L., H.C. Price, R.W. O'Conner et al. 2000. Upper respiratory tract toxicity of inhaled methylvinyl ketone in F-344 rats and B6C3F1 mice. Toxicol. Sci 58:182-194.; Eastman Kodak. 1992. Initial submission: Letter from Eastman Kodak to USEPA regarding toxicity studies of 3-buten-2-one with attachments and cover letter dated 9/02/92. Doc #88-920008988.

Test Species/Strain/Number: 5 male and 5 female Fischer-344 rats and $B_6C_3F_1$ mice

Exposure Route/Concentrations/Durations: 0, 0.25, 0.5, 1, 2, 4, or 8 ppm methyl vinyl ketone (MVK) 6 hours/day, 5 days/week for a total of 12 exposures (Morgan et al. 2000);

Effects: Rat (Morgan et al. 2000)
0.5 ppm = NOAEL
1 ppm = LOAEL for slight nasal lesions
2 ppm = nasal cavity necrosis; no lung lesions
4 ppm = nasal cavity and lung necrosis
8 ppm = 100% mortality (10/10 dead or euthanized in moribund condition) after 1 day exposure

Effects: Mouse (Morgan et al. 2000)
0.5 ppm = NOAEL
1 ppm = LOAEL for slight nasal lesions
2 ppm = nasal cavity necrosis
4 ppm = nasal cavity necrosis
8 ppm = 20% mortality (2/10) after 10 days exposure, nasal cavity and lung necrosis.

Effects: Rat (Eastman Kodak 1992; nominal conc.)
2.1 ppm = NOAEL
3.9 ppm = 20% mortality (2/10) after 8 days, eye irritation
7.8 ppm = 90% mortality within 9 days, eye irritation

Effects: Guinea pig (Eastman Kodak 1992; nominal conc.)
2.1 ppm = NOAEL
3.9 ppm = airway lesions (6/6) , eye irritation; no deaths
7.8 ppm = airway lesions (6/6); 5/6 acute pneumonitis; no deaths

Effects: Rabbit (Eastman Kodak 1992; nominal conc.)
2.1 ppm = NOAEL
3.9 ppm = 1/3 mortality within 9 days, eye irritation
7.8 ppm = 3/3 acute pneumonitis, no mortality, eye irritation

Endpoint/Concentration/Rationale: Point of departure = 4 ppm. 100% incidence of mortality in rats after a single exposure to 8 ppm MVK and 2/5 male mice died after ten exposures to this concentration (Morgan et al. 2000). There were no deaths in rats or mice exposed to 4 ppm for 12 days. The studies conducted in 1973 and reported by Eastman Kodak (1992) showed 20% mortality in rats after 8 days of exposure to 3.9 ppm (all concentrations nominal), 90% mortality after nine days exposure to 7.8 ppm, but no mortality after 10 days exposure to 2.1 ppm. In this same study there were no deaths in guinea pigs after nine days exposure at either 3.9 or 7.8 ppm, no deaths in rabbits at 7.8 ppm, though 1/3 rabbits died after 9 days exposure to 3.9 ppm.

Uncertainty Factors/Rationale: Uncertainty factor of 3 was used for intraspecies variability. A factor of 10 was considered unnecessary since the toxic effects of MVK are related to contact irritation. Responses will not vary substantially among individuals, and do not appear to vary substantially between species since the dose-response relationship was similar in both rats and mice. This is typical for agents that cause irritant effects.
Total uncertainty factor: 3
Interspecies: 1
Intraspecies: 3

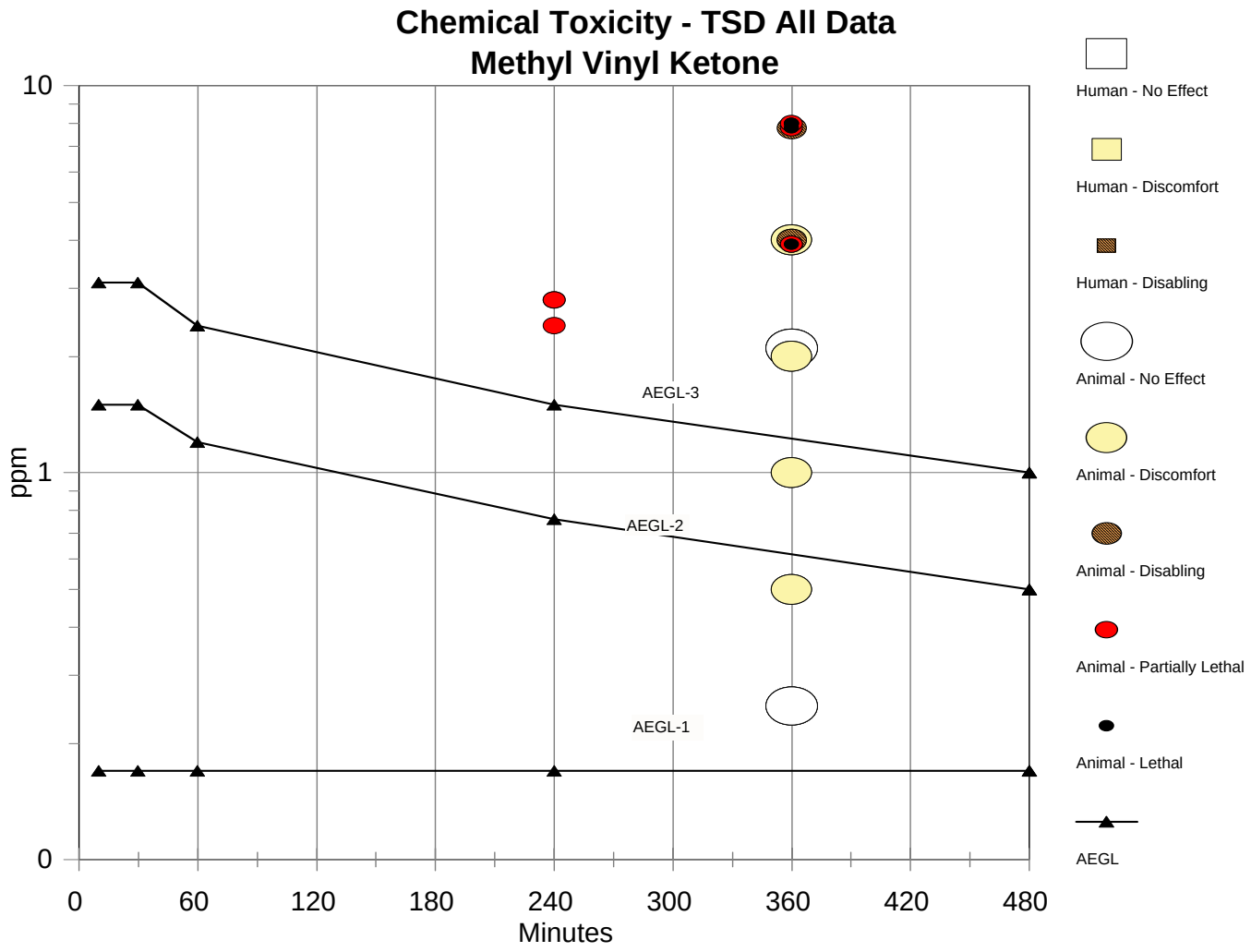
Modifying Factor: None

Animal to Human Dosimetric Adjustment: None

Time Scaling: Temporal scaling was performed using n = 3 when extrapolating to time points ≤6 hours, and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

Data Adequacy: Well conducted animal studies. Eastman Kodak et al. (1992) reported only nominal exposure concentrations.

APPENDIX C: Category Plot for Methyl Vinyl Ketone


Chemical Toxicity - TSD All Data
Methyl Vinyl Ketone
10
1
0
ppm
0
60
120
180
240
300
360
420
480
Minutes
AEGL-3
AEGL-2
AEGL-1
Human - No Effect
Human - Discomfort
Human - Disabling
Animal - No Effect
Animal - Discomfort
Animal - Disabling
Animal - Partially Lethal
Animal - Lethal
AEGL